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L6	L5 same 12	30	L6
L5	radiopa$	11063	L5
L4	13 same 12	16	L4
L3	disinfecting or hydrogen peroxide or endotoxin	151327	L3
L2	submucosa	1380	L2
L1	submusosa	0	L1

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L7: Entry 2 of 3 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020099448 A1
TITLE: MULTI-FORMED COLLAGENOUS BIOMATERIAL MEDICAL DEVICE

Detail Description Paragraph:
[0079] The collagen biomaterial can be made radiopaque by a variety of conventional procedures, none of which has yet been applied to tela submucosa. In one embodiment of the invention, the collagen material has a shape, namely made into sheets, either in lyophilized or non-lyophilized form. With reference to FIGS. 1, 2A, and 2B, any radiopaque substance 40, including but not limited to, tantalum such as tantalum powder, can be spread along the surface of the tela submucosa, such as on the serosal side. Other radiopaque materials 40 comprise bismuth and barium, including but not limited to, bismuth oxychloride and barium sulphate, as well as other conventional markers. As used herein, the term "disposed" on shall be construed to include disposed on, disposed throughout, disposed in, disposed with, disposed along with, applied on, applied with, applied through, applied in, applied in conjunction with, and the like. With particular reference to tela submucosa, the differential porosity of the material can enable more radiopaque material 40 to be disposed on the tela submucosa.

Detail Description Paragraph:
[0080] In one particular embodiment, radiopaque marker tantalum powder was disposed on a sheet of tela submucosa by rubbing it onto the serosal side of the tela submucosa. The tela submucosa was then made into various shapes, such as, but not limited to, having the shape of a brush-like, braided, branched, helical, spherical, cubic, cylindrical, tubular, injectable, randomized, layered, and sheet-like shapes. For example, an injectable shape of the invention can be readily made by comminuting the invention into small fibrils, fragments, or the like, then suspending them in solution, such as, but not limited to, a biocompatible gelatin suspension. Due to the viscosity of the gelatin suspension, the invention, when injected into the lumen of an aneurysm, will stay in the lumen and provide the therapeutic benefit to the aneurysm.

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L6: Entry 10 of 30 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020099448 A1
TITLE: MULTI-FORMED COLLAGENOUS BIOMATERIAL MEDICAL DEVICE

Detail Description Paragraph:
[0079] The collagen biomaterial can be made radiopaque by a variety of conventional procedures, none of which has yet been applied to tela submucosa. In one embodiment of the invention, the collagen material has a shape, namely made into sheets, either in lyophilized or non-lyophilized form. With reference to FIGS. 1, 2A, and 2B, any radiopaque substance 40, including but not limited to, tantalum such as tantalum powder, can be spread along the surface of the tela submucosa, such as on the serosal side. Other radiopaque materials 40 comprise bismuth and barium, including but not limited to, bismuth oxychloride and barium sulphate, as well as other conventional markers. As used herein, the term "disposed" on shall be construed to include disposed on, disposed throughout, disposed in, disposed with, disposed along with, applied on, applied with, applied through, applied in, applied in conjunction with, and the like. With particular reference to tela submucosa, the differential porosity of the material can enable more radiopaque material 40 to be disposed on the tela submucosa.

Detail Description Paragraph:
[0080] In one particular embodiment, radiopaque marker tantalum powder was disposed on a sheet of tela submucosa by rubbing it onto the serosal side of the tela submucosa. The tela submucosa was then made into various shapes, such as, but not limited to, having the shape of a brush-like, braided, branched, helical, spherical, cubic, cylindrical, tubular, injectable, randomized, layered, and sheet-like shapes. For example, an injectable shape of the invention can be readily made by comminuting the invention into small fibrils, fragments, or the like, then suspending them in solution, such as, but not limited to, a biocompatible gelatin suspension. Due to the viscosity of the gelatin suspension, the invention, when injected into the lumen of an aneurysm, will stay in the lumen and provide the therapeutic benefit to the aneurysm.

CLAIMS:

7. The collagenous biomaterial of claim 6 wherein a radiopaque marker is disposed on the submucosa.

16. The collagenous biomaterial of claim 15 wherein a radiopaque marker is disposed on the submucosa.

26. The collagenous biomaterial of claim 25, wherein a pharmacologic agent and a radiopaque marker are disposed on the submucosa.

L6: Entry 23 of 30 File: USPT Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096070 A
TITLE: Coated implantable medical device

Detailed Description Text (18):
A wide range of other bioactive materials can be delivered by the device 10. Accordingly, it is preferred that the bioactive material contained in the layer 18 includes at least one of heparin, covalent heparin, or another thrombin inhibitor, hirudin, hirulog, argatroban, D-phenylalanyl-L-poly-L-arginyl chloromethyl ketone, or another antithrombogenic agent, or mixtures thereof; urokinase, streptokinase, a tissue plasminogen activator, or another thrombolytic agent, or mixtures thereof; a fibrinolytic agent; a vasospasm inhibitor; a calcium channel blocker, a nitrate, nitric oxide, a nitric oxide promoter or another vasodilator; Hytrin.RTM. or other antihypertensive agents; an antimicrobial agent or antibiotic; aspirin, ticlopidine, a glycoprotein IIb/IIIa inhibitor or another inhibitor of surface glycoprotein receptors, or another antiplatelet agent; colchicine or another antimitotic, or another microtubule inhibitor, dimethyl sulfoxide (DMSO), a retinoid or another antisecretory agent; cytochalasin or another actin inhibitor; or a remodelling inhibitor; deoxyribonucleic acid, an antisense nucleotide or another agent for molecular genetic intervention; methotrexate or another antimetabolite or antiproliferative agent; tamoxifen citrate, Taxol.RTM. or the derivatives thereof, or other anti-cancer chemotherapeutic agents; dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate or another dexamethasone derivative, or another anti-inflammatory steroid or non-steroidal anti-inflammatory agent; cyclosporin or another immunosuppressive agent; trapidal (a PDGF antagonist), angiopeptin (a growth hormone antagonist), angiogenin, a growth factor or an anti-growth factor antibody, or another growth factor antagonist; dopamine, bromocriptine mesylate, pergolide mesylate or another dopamine agonist; .sup.60 Co (5.3 year half life), .sup.192 Ir (73.8 days), .sup.32 P (14.3 days), .sup.111 In (68 hours), .sup.90 Y (64 hours), .sup.99m Tc (6 hours) or another radiotherapeutic agent; iodine-containing compounds, barium-containing compounds, gold, tantalum, platinum, tungsten or another heavy metal functioning as a radiopaque agent; a peptide, a protein, an enzyme, an extracellular matrix component, a cellular component or another biologic agent; captopril, enalapril or another angiotensin converting enzyme (ACE) inhibitor; ascorbic acid, alpha tocopherol, superoxide dismutase, deferoxamine, a 21-aminosteroid (lasaroid) or another free radical scavenger, iron chelator or antioxidant; a .sup.14 C-, .sup.3 H-, .sup.131 I-, .sup.32 P- or .sup.36 S-radiolabelled form or other radiolabelled form of any of the foregoing; estrogen or another sex hormone; AZT or other antipolymerases; acyclovir, famciclovir, rimantadine hydrochloride, ganciclovir sodium, Norvir, Crixivan, or other antiviral agents; 5-aminolevulinic acid, meta-tetrahydroxyphenylchlorin, hexadecafluoro zinc phthalocyanine, tetramethyl hematoporphyrin, rhodamine 123 or other photodynamic therapy agents; an IgG2 Kappa antibody against Pseudomonas aeruginosa exotoxin A and reactive with A431 epidermoid carcinoma cells, monoclonal antibody against the noradrenergic enzyme dopamine beta-hydroxylase conjugated to saporin or other antibody targeted therapy agents; gene therapy agents; and enalapril and other prodrugs; Proscar.RTM., Hytrin.RTM. or other agents for treating benign prostatic hyperplasia (BHP) or a mixture of any of these; and various forms of small intestine submucosa (SIS).

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L6: Entry 26 of 30 File: USPT Feb 23, 1999

DOCUMENT-IDENTIFIER: US 5873904 A
TITLE: Silver implantable medical device

Detailed Description Text (17):
A wide range of other bioactive materials can be delivered by the device 10. Accordingly, it is preferred that the bioactive material contained in the layer 18 includes at least one of heparin, covalent heparin, or another thrombin inhibitor, hirudin, hirulog, argatroban, D-phenylalanyl-L-poly-L-arginyl chloromethyl ketone, or another antithrombogenic agent, or mixtures thereof; urokinase, streptokinase, a tissue plasminogen activator, or another thrombolytic agent, or mixtures thereof; a fibrinolytic agent; a vasospasm inhibitor; a calcium channel blocker, a nitrate, nitric oxide, a nitric oxide promoter or another vasodilator; Hytrin.RTM. or other antihypertensive agents; an antimicrobial agent or antibiotic; aspirin, ticlopidine, a glycoprotein IIb/IIIa inhibitor or another inhibitor of surface glycoprotein receptors, or another antiplatelet agent; colchicine or another antimitotic, or another microtubule inhibitor, dimethyl sulfoxide (DMSO), a retinoid or another antisecretory agent; cytochalasin or another actin inhibitor; or a remodeling inhibitor; deoxyribonucleic acid, an antisense nucleotide or another agent for molecular genetic intervention; methotrexate or another antimetabolite or antiproliferative agent; tamoxifen citrate, Taxol.RTM. or the derivatives thereof, or other anti-cancer chemotherapeutic agents; dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate or another dexamethasone derivative, or another antiinflammatory steroid or non-steroidal antiinflammatory agent; cyclosporin or another immunosuppressive agent; trapidal (a PDGF antagonist), angiopeptin (a growth hormone antagonist), angiogenin, a growth factor or an anti-growth factor antibody, or another growth factor antagonist; dopamine, bromocriptine mesylate, pergolide mesylate or another dopamine agonist; .sup.60 Co (5.3 year half life), .sup.192 Ir (73.8 days), .sup.32 P (14.3 days), .sup.111 In (68 hours), .sup.90 Y (64 hours), .sup.99m Tc (6 hours) or another radiotherapeutic agent; iodine-containing compounds, barium-containing compounds, gold, tantalum, platinum, tungsten or another heavy metal functioning as a radiopaque agent; a peptide, a protein, an enzyme, an extracellular matrix component, a cellular component or another biologic agent; captopril, enalapril or another angiotensin converting enzyme (ACE) inhibitor; ascorbic acid, alpha tocopherol, superoxide dismutase, deferoxamine, a 21-aminosteroid (lasaroid) or another free radical scavenger, iron chelator or antioxidant; a .sup.14 C-, .sup.3 H-, .sup.131 I-, .sup.32 P- or .sup.36 S-radio labeled form or other radio labeled form of any of the foregoing; estrogen or another sex hormone; AZT or other antipolymerases; acyclovir, famciclovir, rimantadine hydrochloride, ganciclovir sodium, Norvir, Crixivan, or other antiviral agents; 5-aminolevulinic acid, meta-tetrahydroxyphenylchlorin, hexadecafluoro zinc phthalocyanine, tetramethyl hematoporphyrin, rhodamine 123 or other photodynamic therapy agents; an IgG2 Kappa antibody against Pseudomonas aeruginosa exotoxin A and reactive with A431 epidermoid carcinoma cells, monoclonal antibody against the noradrenergic enzyme dopamine beta-hydroxylase conjugated to saporin or other antibody targeted therapy agents; gene therapy agents; and enalapril and other prodrugs; Proscar.RTM., Hytrin.RTM. or other agents for treating benign prostatic hyperplasia (BHP) or a mixture of any of these; and various forms of small intestine submucosa (SIS).

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L4: Entry 9 of 16 File: USPT Mar 19, 2002

DOCUMENT-IDENTIFIER: US 6358284 B1
TITLE: Tubular grafts from purified submucosa

Detailed Description Text (15):
Tela submucosa, as with many animal tissues, is generally aseptic in its natural state, provided the human or animal does not have an infection or disease. This is particularly the case since the tela submucosa is an internal layer within the alimentary, respiratory, urinary and genital tracts of animals. Accordingly, it is generally not exposed to bacteria and other cellular debris such as the epithelium of the intestinal tract. One feature of the present invention is the discovery that by disinfecting the source tissue for the tela submucosa prior to delamination, the aseptic state of the tela submucosa layer can be preserved or substantially preserved, particularly if the delamination process occurs under sterile conditions.

Detailed Description Text (16):
In particular, it has been discovered that disinfecting the tela submucosa source, followed by removal of a purified matrix including the tela submucosa, e.g. by delaminating the tela submucosa from the tunica muscularis and the tunica mucosa, minimizes the exposure of the tela submucosa to bacteria and other contaminants. In turn, this enables minimizing exposure of the isolated tela submucosa matrix to disinfectants or sterilants if desired, thus substantially preserving the inherent biochemistry of the tela submucosa and many of the tela submucosa's beneficial effects.

Detailed Description Text (17):
A tela submucosa implantable collagen matrix according to the present invention can, as indicated above, be obtained from the alimentary, respiratory, urinary or genital tracts of animals. Preferably, the tela submucosa tissues, which are collagen-based and thus predominantly collagen, are derived from the alimentary tract of mammals and most preferably from the intestinal tract of pigs. A most preferred source of whole small intestine is harvested from mature adult pigs weighing greater than about 450 pounds. Intestines harvested from healthy, nondiseased animals will contain blood vessels and blood supply within the intestinal tract, as well as various microbes such as E. coli contained within the lumen of the intestines. Therefore, disinfecting the whole intestine prior to delamination of the tela submucosa substantially removes these contaminants and provides a preferred implantable tela submucosa tissue which is substantially free of blood and blood components as well as any other microbial organisms, pyrogens or other pathogens that may be present. In effect, this procedure is believed to substantially preserve the inherent aseptic state of the tela submucosa, although it should be understood that it is not intended that the present invention be limited by any theory.

Detailed Description Text (19):
As discussed above, it has been discovered that a highly pure form of an implantable tela submucosa collagen matrix may be obtained by first disinfecting a tela submucosa source prior to removing a purified collagen matrix including the tela submucosa layer, e.g. by delaminating the tela submucosa source. It has also been discovered that certain processing advantages as well as improved properties

of the resultant tela submucosa layer are obtained by this process, including greater ease in removing attached tissues from the submucosa layer, and a characteristic, low contaminant profile.

CLAIMS:

1. A unitary multi-layered graft prosthesis comprising a first sheet of a collagen-based matrix structure removed from a submucosa tissue source and having an endotoxin level less than 12 endotoxin units per gram, the first sheet having a first edge and a second opposite edge, formed in the shape of a tube, wherein the second opposite edge of the first sheet extends over the first edge of the first sheet to define a multiple layered overlapped region, wherein the layers in the overlapped region are fixed to one another; and

a second sheet of a collagen-based matrix structure removed from a submucosa tissue source and having an endotoxin level less than 12 endotoxin units per gram, the second sheet having a first edge and a second opposite edge, wherein said second sheet is in adherent contact with the tube of said first sheet and the first edge and second opposite edge of the second sheet are joined together along the length of the tube without perforating the underlying tube of said first sheet.

15. A unitary multi-layered graft prosthesis comprising a sheet of a purified collagen-based matrix structure removed from a submucosa tissue source and having an endotoxin level less than 12 endotoxin units per gram, the sheet having a first edge and a second opposite edge, formed in the shape of a tube, wherein the second opposite edge of the sheet extends over the first edge of the sheet to define a multiple layered overlapped region, wherein the layers in the overlapped region are fixed to one another.

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L4: Entry 10 of 16 File: USPT Mar 27, 2001

DOCUMENT-IDENTIFIER: US 6206931 B1
TITLE: Graft prosthesis materials

Brief Summary Text (12):
Another preferred embodiment of the invention provides a graft prosthesis which includes a purified, collagen-based matrix structure removed from a submucosa tissue source, wherein the purified structure has an endotoxin level of less than 12 endotoxin units per gram. The purified structure may have an endotoxin level of less than 1 endotoxin unit per gram, and even less than 0.5 endotoxin units per gram.

Brief Summary Text (16):
A further embodiment of the invention concerns a method for obtaining a collagen-based matrix from a submucosa tissue source. The method includes treating the submucosa tissue source with a disinfecting agent to provide a disinfected submucosa tissue source, and removing the collagen-based matrix from the disinfected submucosa tissue source.

Brief Summary Text (17):
Another preferred embodiment of the invention provides a method for obtaining a collagen-based matrix from a submucosa tissue source, which includes providing a submucosa tissue source which has been treated with a disinfecting agent, and removing the collagen-based matrix from the submucosa tissue source.

Brief Summary Text (19):
Also provided by the present invention is a purified collagen-containing matrix obtained from a mammalian tissue source, the matrix including mammalian tela submucosa and being obtainable by a process which includes disinfecting the mammalian tissue source then removing the structure from the resulting disinfected mammalian tissue source.

Brief Summary Text (21):
Further in accordance with the present invention, a purified delaminated tela submucosa collagen matrix is provided which is derived from the alimentary, respiratory, urinary or genital tracts of animals or humans, wherein said purified submucosa collagen matrix is produced by delaminating a disinfected tela submucosa source to obtain the delaminated tela submucosa collagen matrix. An advantageous matrix may be obtained, for example, by a process comprising treating an unprocessed, undelaminated tela submucosa source harvested from the alimentary, respiratory, urinary or genital tracts of animals with a disinfecting agent, followed by delaminating the tela submucosa collagen matrix from the attached tissues. The preferred collagen matrix has a bioburden level of substantially zero and capable of being implanted within a human or animal patient without causing a cytotoxic response, infection, rejection of the implant or any other harmful effect in a majority of patients.

Brief Summary Text (22):
Still further in accordance with the present invention, a method is provided for obtaining a highly pure, delaminated tela submucosa collagen matrix in a substantially sterile state, comprising delaminating a disinfected tela submucosa

tissue source to obtain the delaminated tela submucosa collagen matrix. A preferred method comprises treating an undelaminated tela submucosa source harvested from the alimentary, respiratory, urinary or genital tracts of animals or humans with a disinfecting agent, followed by delaminating the tela submucosa from its other source tissues attached to the tela submucosa.

Brief Summary Text (24):
Still further in accordance with the present invention, a highly pure tela submucosa is provided which is derived from the alimentary, respiratory, urinary or genital tracts of animals and wherein the tela submucosa is delaminated in a substantially sterile condition comprising growth factors, and is produced by rinsing the delaminated, tela submucosa source with a solvent, for instance water, followed by treatment with a disinfecting agent, preferably a peracid, at a pH of about 1.5 to about 10 followed by delamination of the tela submucosa from the attached tissues. The peracid is buffered at pH levels greater than 7. Desirably, collagen matrices so produced have a substantial high content of one or more growth factors.

Brief Summary Text (25):
Still further in accordance with the present invention, provided is a tissue graft composition which includes a tela submucosa collagen matrix which is essentially pyrogen free. More preferred such compositions will include a tela submucosa collagen matrix which has a pyrogen content of about 1 endotoxin unit per gram (EU/g) or less.

Detailed Description Text (14):
Tela submucosa, as with many animal tissues, is generally aseptic in its natural state, provided the human or animal does not have an infection or disease. This is particularly the case since the tela submucosa is an internal layer within the alimentary, respiratory, urinary and genital tracts of animals. Accordingly, it is generally not exposed to bacteria and other cellular debris such as the epithelium of the intestinal tract. One feature of the present invention is the discovery that by disinfecting the source tissue for the tela submucosa prior to delamination, the aseptic state of the tela submucosa layer can be preserved or substantially preserved, particularly if the delamination process occurs under sterile conditions.

Detailed Description Text (15):
In particular, it has been discovered that disinfecting the tela submucosa source, followed by removal of a purified matrix including the tela submucosa, e.g. by delaminating the tela submucosa from the tunica muscularis and the tunica mucosa, minimizes the exposure of the tela submucosa to bacteria and other contaminants. In turn, this enables minimizing exposure of the isolated tela submucosa matrix to disinfectants or sterilants if desired, thus substantially preserving the inherent biochemistry of the tela submucosa and many of the tela submucosa's beneficial effects.

Detailed Description Text (16):
A tela submucosa implantable collagen matrix according to the present invention can, as indicated above, be obtained from the alimentary, respiratory, urinary or genital tracts of animals. Preferably, the tela submucosa tissues, which are collagen-based and thus predominantly collagen, are derived from the alimentary tract of mammals and most preferably from the intestinal tract of pigs. A most preferred source of whole small intestine is harvested from mature adult pigs weighing greater than about 450 pounds. Intestines harvested from healthy, nondiseased animals will contain blood vessels and blood supply within the intestinal tract, as well as various microbes such as E. coli contained within the lumen of the intestines. Therefore, disinfecting the whole intestine prior to delamination of the tela submucosa substantially removes these contaminants and provides a preferred implantable tela submucosa tissue which is substantially free

of blood and blood components as well as any other microbial organisms, pyrogens or other pathogens that may be present. In effect, this procedure is believed to substantially preserve the inherent aseptic state of the tela submucosa, although it should be understood that it is not intended that the present invention be limited by any theory.

Detailed Description Text (18):
As discussed above, it has been discovered that a highly pure form of an implantable tela submucosa collagen matrix may be obtained by first disinfecting a tela submucosa source prior to removing a purified collagen matrix including the tela submucosa layer, e.g. by delaminating the tela submucosa source. It has also been discovered that certain processing advantages as well as improved properties of the resultant tela submucosa layer are obtained by this process, including greater ease in removing attached tissues from the submucosa layer, and a characteristic, low contaminant profile.

Detailed Description Text (19):
Processes of the invention desirably involve first rinsing the tela submucosa source one or more times with a solvent, suitably water. The rinsing step is followed by treatment with a disinfecting agent. The disinfecting agent is desirably an oxidizing agent. Preferred disinfecting agents are peroxy compounds, preferably organic peroxy compounds, and more preferably peracids. Such disinfecting agents are desirably used in a liquid medium, preferably a solution, having a pH of about 1.5 to about 10, more preferably a pH of about 2 to about 6, and most preferably a pH of about 2 to about 4. In methods of the present invention, the disinfecting agent will generally be used under conditions and for a period of time which provide the recovery of characteristic, purified submucosa matrices as described herein, preferably exhibiting a bioburden of essentially zero and/or essential freedom from pyrogens. In this regard, desirable processes of the invention involve immersing the tissue source (e.g. by submersing or showering) in a liquid medium containing the disinfecting agent for a period of at least about 5 minutes, typically in the range of about 5 minutes to about 40 hours, and more typically in the range of about 0.5 hours to about 5 hours.

Detailed Description Text (21):
A preferred organic peroxide disinfecting agent is perpropionic acid. The concentration of perpropionic acid may range from about 0.1% to 10% by volume. More preferably the perpropionic acid concentration is from about 0.1% to 1.0% by volume and most preferably from about 0.2% to 0.5% by volume. These concentrations of perpropionic acid can be diluted in water or in an aqueous solution of about 2% to about 30% by volume alcohol. Most preferably the alcohol is ethanol. The tela submucosa tissue source can be exposed to the organic peroxide solution for periods from about 15 minutes to about 40 hours, and more typically in the range of about 0.5 hours to about 8 hours. Other peroxy disinfecting agents are suitable for use as described in "Peroxygen Compounds", S. Block, in Disinfection, Sterilization and Preservation, S. Block, Editor, 4th Edition, Philadelphia, Lea & Febiger, pp. 167-181, 1991; and "Disinfection with peroxygens", M. G. C. Baldry and J. A. L. Fraser, in Industrial Biocides, K. Payne, Editor, New York, John Wiley and Sons, pp. 91-116, 1988.

Detailed Description Text (24):
When a peracid is used in the disinfection, it is preferably selected from the group consisting of peracetic acid, perpropionic acid or perbenzoic acid. Peracetic acid is the most preferred disinfecting agent. The peracetic acid is preferably diluted into about a 2% to about 10% by volume alcohol solution. The concentration of the peracetic acid may range, for example, from about 0.05% by volume to about 1.0% by volume. Most preferably the concentration of the peracetic acid is from about 0.1% to about 0.3% by volume. Hydrogen peroxide can also be used as a disinfecting agent. Alternatively, or in addition, the tela submucosa tissue source, e.g. from small intestine, may be disinfected utilizing disinfecting agents

such as glutaraldehyde, formalin and the like, which are also known for their ability to introduce substantial crosslinking into collagen matrices, in contrast to the action of other disinfecting agents such as peracids which can be used to disinfect without introducing such crosslinking. Additionally, the tela submucosa source can be treated with radiation, e.g., gamma radiation, for purposes of disinfection.

Detailed Description Text (31):
Following the treatment as described above, the tela submucosa layer is delaminated from its source, e.g., whole intestine, cow uterus and the like. It has been found that by following this post-disinfection-stripping procedure, it is easier to separate the tela submucosa layer from the attached tissues, e.g. at least from attached tunica muscularis tissue, as compared to stripping the tela submucosa layer prior to disinfection. Moreover it has been discovered that the resultant tela submucosa layer in its most preferred form exhibits superior histology, in that there is less attached tissue and debris on the surface compared to a tela submucosa layer obtained by first delaminating the tela submucosa layer from its source and then disinfecting the layer. Moreover, a more uniform tela submucosa tissue can be obtained from this process, and a tela submucosa having the same or similar physical and biochemical properties can be obtained more consistently from each separate processing run. Importantly, a highly purified, substantially sterile tela submucosa is obtained by this process.

Detailed Description Text (33):
It has also been discovered that more preferred processes according to the present invention, not only will eliminate or significantly reduce contaminants contained in the tela submucosa collagen matrix, but also will produce a tissue which exhibits no substantial degradation of physical and mechanical properties, e.g., differential porosity (i.e. wherein one side of the submucosa layer has greater porosity than the other side), and good strength, for example burst strength. Also, it has been discovered that more preferred processes do not affect the differential porosity of the tela submucosa collagen matrix which ultimately affects the level of efficacy of this tissue implant. For example, the tissue is not necessarily treated with a crosslinking agent or a material that disrupts the porosity or inherent, native structure of the collagen matrix. Moreover, when hydrogen peroxide is employed, the matrix as a whole has greater porosity as well as a higher oxygen content. This helps to ensure the absence of contaminants e.g., endotoxins, pyrogens and the like.

Detailed Description Text (62):
Thirty feet of whole intestine from a mature adult hog is rinsed with water. This material is then treated in a 0.2 percent by volume peracetic acid in a 5 percent by volume aqueous ethanol solution for a period of two hours with agitation. The tela submucosa layer is then delaminated in a disinfected casing machine from the whole intestine. The delaminated tela submucosa is rinsed four (4) times with sterile water and tested for impurities or contaminants such as endotoxins, microbial organisms, and pyrogens. The resultant tissue was found to have essentially zero bioburden level. The tela submucosa layer separated easily and consistently from the whole intestine and was found to have minimal tissue debris on its surface.

Detailed Description Text (68):
Two sections of small intestine are processed by differing methods. The first section is rinsed in tap water, disinfected for 2 hours in a 5% by volume aqueous ethanol solution comprising 0.2% by volume peracetic acid, pH approximately 2.6, delaminated to the tela submucosa, rinsed in purified water, divided into two samples and rapidly frozen. The second section is rinsed in tap water, delaminated to the tela submucosa, rinsed in purified water, placed in a 10% neomycin sulfate solution for 20 minutes (as described in U.S. Pat. No. 4,902,508), rinsed in purified water, divided into two samples and rapidly frozen. The four above-

prepared samples are tested for bioburden and endotoxin levels. The first two samples each have bioburdens of less than 0.1 CFU/g and endotoxin levels of less than 0.1 EU/g. The second two samples have respective bioburdens of 1.7 CFU/g and 2.7 CFU/g and respective endotoxin levels of 23.9 EU/g and 15.7 EU/g.

Detailed Description Text (70):
Three sections of small intestine are processed by differing methods. The first is rinsed in tap water, disinfected for 2 hours in a 5% by volume aqueous ethanol solution comprising 0.2% by volume peracetic acid, pH about 2.6, delaminated to the tela submucosa, rinsed in purified water, and rapidly frozen. The second is rinsed in tap water, delaminated to the tela submucosa, rinsed in purified water, disinfected according to the methods of Example 1 in U.S. Pat. No. 5,460,962 (treatment for 40 hours in a 0.1% by volume aqueous solution of peracetic acid, buffered to pH 7.2), and rapidly frozen. The third is rinsed in tap water, delaminated to the tela submucosa, rinsed in purified water, disinfected according to the methods of Example 2 in U.S. Pat. No. 5,460,962 (treatment in 0.1% by volume peracetic acid in high salt solution, buffered to pH 7.2), and rapidly frozen. All three samples were tested for endotoxins. The endotoxin levels were <0.14 EU/g for the first sample, >24 EU/g for the second sample, and >28 EU/g for the third sample.

Detailed Description Text (77):
Sections of tela submucosa prepared according to the methods described herein were sent to an independent testing laboratory (NamSA, Inc., Northwood, Ohio) for biocompatibility testing as described in the standard ISO 10993. The samples were tested for USP Acute Systemic Toxicity, USP Intracutaneous Toxicity, Cytotoxicity, LAL Endotoxin, material-mediated Pyrogenicity, Direct Contact Hemolysis, and Primary Skin Irritation. The samples passed all tests, indicating that the material is biocompatible.

Detailed Description Text (78):
It will be appreciated that variations of the above-described processing procedures are intended to be within the scope of this invention. For example, the source tissue for the tela submucosa, e.g., stomach, whole intestine, cow uterus and the like, can be partially delaminated, treated with a disinfecting or sterilizing agent followed by complete delamination of the tela submucosa. Illustratively, attached mesentery layers, and/or serosa layers of whole intestine can be advantageously removed prior to treatment with the disinfecting agent, followed by delamination of remaining attached tissues from the tela submucosa. These steps may or may not be followed by additional disinfection steps, e.g., enzymatic purification and/or nucleic acid removal. Alternatively, the tela submucosa source can be minimally treated with a disinfecting or other such agent, the tela submucosa delaminated from the tunica muscularis and tunica mucosa, followed by a complete disinfection treatment to attain the desired contaminant level(s). All such variations and modifications are contemplated to be a part of the process described herein and to be within the scope of the invention.

CLAIMS:

1. A graft prosthesis, comprising:

a purified, collagen-based matrix structure removed from a submucosa tissue source, said purified structure having a contaminant level making said purified structure biocompatible, said purified structure further having an endotoxin level of less than 12 endotoxin units per gram.

22. A graft prosthesis comprising:

a purified, collagen-based matrix structure removed from a submucosa tissue source, said purified structure having an endotoxin level of less than 12 endotoxin units

per gram.

23. A graft prosthesis, comprising:

a purified, collagen-based matrix structure removed from a submucosa tissue source, said purified structure having a nucleic acid content level of less than 2 micrograms per milligram and an endotoxin level of less than 12 endotoxin units per gram.

24. A graft prosthesis comprising:

a purified, collagen-based matrix structure removed from a submucosa tissue source, said purified structure having a virus level of less than 500 plaque forming units per gram and an endotoxin level of less than 12 endotoxin units per gram.

25. A graft prosthesis comprising:

a purified, collagen-based matrix structure removed from a submucosa tissue source, said purified structure having a processing agent level of less than 100,000 parts per million per kilogram and an endotoxin level of less than 12 endotoxin units per gram.

34. A graft prosthesis, comprising:

a purified collagen-containing matrix obtained from a mammalian tissue source, said matrix comprising tela submucosa and residual contaminants from said mammalian tissue source, said matrix obtainable by a process which comprises disinfecting said mammalian tissue and then removing said matrix from the disinfected mammalian tissue, said matrix having an endotoxin level of less than 12 endotoxin units Per gram.